Rejection Under 35 U.S.C. § 112, second paragraph

In paragraphs 6a and 6b (pages 3-4) of Paper No. 6, the Examiner rejected claims 1-13 and 20-24 under 35 U.S.C. § 112, second paragraph as being "indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention." Paper No. 6, paragraph 6 at page 3. Specifically, the Examiner expressed concern over the terms "in a single phase" and "proportional." Applicants respectfully traverse this rejection.

The Examiner indicated that claims 1-13 and 20-24 are vague and indefinite because the phrase "in a single phase" is unclear. The Examiner suggested that the term may mean the amplification occurs "in a single steps or in a solution phase or on a solid support." Paper No. 6, paragraph 6a at page 3. In the specification, e.g., at page 5, lines 26-28, Applicants define the term in question. The specification discloses that "at least three otherwise separate enzymatic reactions can occur consecutively in one phase (*i.e.*, without organic extraction and precipitation), more preferably in the same reaction vessel." Furthermore, a reaction vessel may include a membrane, filter, microscope slide, microwell, sample tube, array or the like. (see specification at page 6, lines 18-19). Thus, the term "in a single phase" encompasses the enzymatic reactions of nucleic acid amplification wherein the reactions occur in a single reaction vessel.

In rendering the rejection, the Examiner also indicated that the term "proportional" in claim 2 is unclear. Paper No. 6, paragraph 6b at page 4. The Examiner stated that there are two steps in the amplification process, "one is to synthesize double-stranded DNA and the second step is to produce multiple copies of RNA" and that it is unclear which amplification step is proportional. In addition, the Examiner suggested that the term may mean the amplification is linear or exponential.

Without acquiescing to the propriety of the present rejection, claim 2 has been canceled and the limitation of this claim has been incorporated into claim 1. Thus, claim 1 has been amended to specify that the amplification method is proportional and therefore, the term "proportional" applies to both amplification steps (i.e., synthesizing double-stranded DNA and producing multiple copies of RNA). In addition, the term "proportional" refers to the exponential amplification of nucleic acids.

It is thus submitted that the claims meet the requirements of 35 USC § 112, second paragraph, and reconsideration and withdrawal of the present rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102: Kwoh et al.

In paragraph 8 (pages 4-5) of Paper No. 6, the Examiner rejected claims 1-12 under 35 U.S.C. § 102(b) as being anticipated by Kwoh et al. Applicants respectfully traverse this rejection.

In order to support anticipation under 35 U.S.C. §102, each and every element of a claimed invention must be disclosed within a single prior art reference. *See In re Bond*, 15 USPQ2d 1896 (Fed. Cir. 1991).

As amended and claimed, the invention relates to a method for single-phase proportional amplification of nucleic acids. Specifically, the independent claim 1 provides a method for the single-phase proportional amplification of nucleic acids which comprises the steps of synthesizing double-stranded DNA from a single-stranded DNA population and producing multiple copies of RNA from the double-stranded DNA. Indeed, the claimed invention relates to the proportional amplification of a population of nucleic acids, which, *inter alia*, limits amplification bias and preserves the relative abundance of the individual nucleic acid species in the original tissue or cell sample. (see specification page 3, lines 19-23; page 7, lines 10-17). The invention also discloses the use of a four-enzyme mix for the amplification steps. (see specification page 3, lines 29-32; page 14, lines 8-16).

Kwoh et al. discloses a method of amplifying a single nucleic acid comprising two steps: a DNA synthesis step and an RNA transcription step. However, Kwoh et al. does not teach or disclose the proportional amplification of a nucleic acid population. Furthermore, Kwoh et al. does not teach or disclose the use of a four-enzyme mix for the amplification steps.

Since the method of nucleic acid amplification described by Kwoh et al. does not disclose the proportional amplification of a population of nucleic acids nor the use of a four-enzyme mix as claimed in the invention, Kwoh et al. does not teach each and every limitation of the claimed invention. Therefore, the Examiner has failed to establish a proper rejection under 35 U.S.C. § 102 (b). Accordingly, Applicants respectfully request reconsideration and withdrawal of the of the present rejection.

Rejection Under 35 U.S.C. § 103(a): Kwoh et al., Goller et al., Compton et al., and Schnipelsky et al.

In paragraph 10 (pages 6-7) of Paper No. 6, the Examiner rejects claims 1 and 13 under U.S.C. § 103(a) as unpatentable over Kwoh et al., in view of Goller et al. In paragraph 11 (page 7) of Paper No. 6, the Examiner rejects claims 1 and 22-24 under U.S.C. § 103(a) as unpatentable over Kwoh et al., in view of Compton. In paragraph 12 (page 8) of Paper No. 6, the Examiner rejects claims 1 and 20-21 under U.S.C. § 103(a) as unpatentable over Kwoh et al., in view of Schnipelsky et al. Applicants respectfully traverse.

To properly maintain a rejection under 35 U.S.C. § 103, three conditions must be met. First, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the prior art must also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in the Applicant's disclosure. Finally, the prior art reference must teach or suggest all the claim limitations. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

As amended, the invention relates to the proportional amplification of a nucleic acid population. The Examiner states that one of ordinary skill "would have been motivated to use RNA from embryonic and tumorigenic as a target as taught by Goller et al. in the method of Kwoh et al. because the expression of the glutaredoxin mRNA could be induced by a jun-estrogen receptor in the absence of *de novo* protein biosynthesis and therefore the oncogene can be studied." Paper No. 6 at pages 6-7. Applicants respectfully traverse.

The method of Goller et al. does not teach or suggest a method for proportional amplification of nucleic acids as claimed. Kwoh et al. relates to the amplification of a single target sequence from HIV-1 infected lymphocytes. Indeed, Kwoh et al. also does not teach or suggest the proportional amplification of a nucleic acid population. Therefore, the teachings of Kwoh et al. in combination with Goller et al. do not teach or suggest the present invention and the requisite reasonable expectation of success is absent. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 1 and 22-24 were rejected as being unpatentable over Kwoh et al. in view of Compton. The Examiner stated that Kwoh et al. "do not disclose a kit which is used to fulfil the amplification process" and Compton "discloses a method of amplifying RNA involving using the kit containing the components and appropriate primers." The Examiner also stated

that one of ordinary skill would have been motivated to combine these references "because the method of Kwoh et al. allows the detection of fewer than one HIV-1 infected lymphocyte cell in a population of 10^6 uninfected lymphocyte cells and the kit of Compton is convenient to perform the method." Paper No. 6 at page 7. Applicants respectfully traverse.

Compton relates to a nucleic acid sequence-based amplification (NASBA) reaction mixture that can be used to directly amplify specific sequences of RNA. However, the reaction mix includes primers for a target sequence. Compton does not teach or suggest the proportional amplification of a nucleic acid population of the present invention. Furthermore, Kwoh et al., as stated above, relates to the amplification of a single target sequence from HIV-1 infected lymphocytes. Kwoh et al. does not teach or suggest the amplification of a population of nucleic acids. Therefore, Kwoh et al. in combination with Compton do not teach or suggest the present invention and the requisite reasonable expectation of success is absent. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 1 and 20-21 were rejected as being unpatentable over Kwoh et al. in view of Schnipelsky et al. As stated by the Examiner, Schnipelsky et al. "disclose an apparatus to amplify a nucleic acid sequence" and the apparatus "involves PCR thermocycler, an integrated reaction device and a robotic delivery system." Paper No. 6 at page 8. Applicants respectfully traverse.

According to the Examiner, one would have been motivated to combine Kwoh et al. and Schnipelsky et al. "because the method of Kwoh et al. allows the detection of fewer than one HIV-1 infected lymphocyte cell in a population of 10^6 uninfected lymphocyte cells and the apparatus of Schnipelsky et al. can prevent sample contamination." Paper No. 6 at page 8. Schnipelsky et al. relates to an apparatus that may be used to amplify and detect DNA. However, Schnipelsky et al. does not teach or suggest an apparatus that may be used to proportionally amplify a population of nucleic acids. As discussed above, Kwoh et al. does not teach or suggest the amplification of a population of nucleic acids. Therefore, the teachings of Kwoh et al. in combination with Schnipelsky et al. do not teach or suggest the present invention and the requisite reasonable expectation of success is absent. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

It is therefore submitted respectfully that Kwoh et al., either singly or in combination with Goller et al., Compton et al., and/or Schnipelsky et al., fails to teach or suggest a method for the single-phase proportional amplification of a population of nucleic acids as presently

claimed, and that the current invention is novel and nonobvious in view of the prior art references. For the foregoing reasons in this section, Applicants respectfully request reconsideration and withdrawal of the present rejections.

CONCLUSION

For the foregoing reasons, Applicants submit that all of the claims are in condition for allowance and Applicants respectfully request reexamination of the present application, reconsideration and withdrawal of the present rejections and entry of the amendments. Should there be any further matter requiring consideration, Examiner Tung is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 50-1067. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account.

Respectfully submitted,

4 January 2001

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Claim Amendments, 4 January 2001

1. (Amended) A method for the amplification of nucleic acids, said method comprising:

synthesizing double-stranded DNA from a single-stranded DNA population, and

producing multiple copies of RNA from said double-stranded DNA,

wherein said amplification occurs in a single phase and wherein said amplification is proportional.